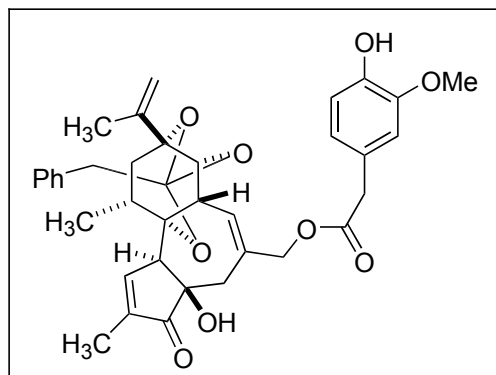


Diastereoselective Phenol para-Alkylation: Access to a Cross-Conjugated Cyclohexadienone en Route to Resiniferatoxin

Carreira, et. Al. Organic Letters, ASAP



Resiniferatoxin (RTX): Therapeutic, Past and Present

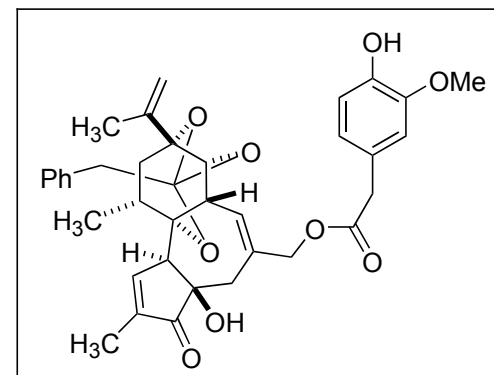
-RTX is taken from the milk of *Euphorbia Resinifera*, a cactus-like plant common to many parts of the world.

-Tradition holds that the great Roman physician Euphorbius used the nectar of *E. Resinifera* to treat Emperor Augustus. Coincidentally, Euphorbius's brother, Antonius Musa, gained Roman immortality by treating Augustus with lettuce extracts combined in cold baths to heal the Emperor at other times. A statue of Musa was placed in the temple of Aesculapius, the god of Roman medicine.

-RTX is historically credited to King Juba II of Mauretania (50 BC - 23 AD), as he described the potency of RTX resin in *On Latex*, which is considered to be the first pharmacological monograph produced. Juba named the plant after Euphorbius, his favorite physician.

-During the Renaissance, RTX resin was overtaken as the preferred method of making someone sneeze by tobacco for healing purposes.

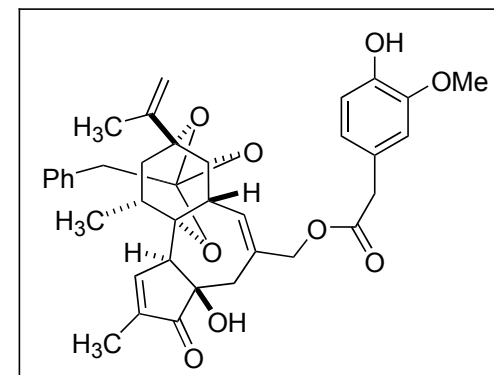
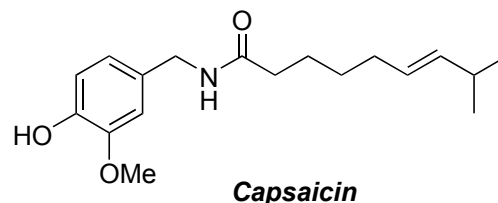
-RTX resin also contains ingenol and 12-deoxy phorbol esters.



For an extensive history of RTX, see: *Life Sci.* **1997**, *60*, 681

Resiniferatoxin (RTX): Therapeutic, Past and Present

-RTX is considered an "ultra-potent capsaicin analogue".



-Naturally, RTX has marked similarities with capsaicin, yet RTX and capsaicin often have very different affinities for biological targets. The predominantly relates to RTX's potency, which tends to deaden a nerve, while capsaicin often has exciting properties.

-RTX (and capsaicin) hit the TRPV1 receptor, a nonselective cation channel, which play roles in several sensory functions.

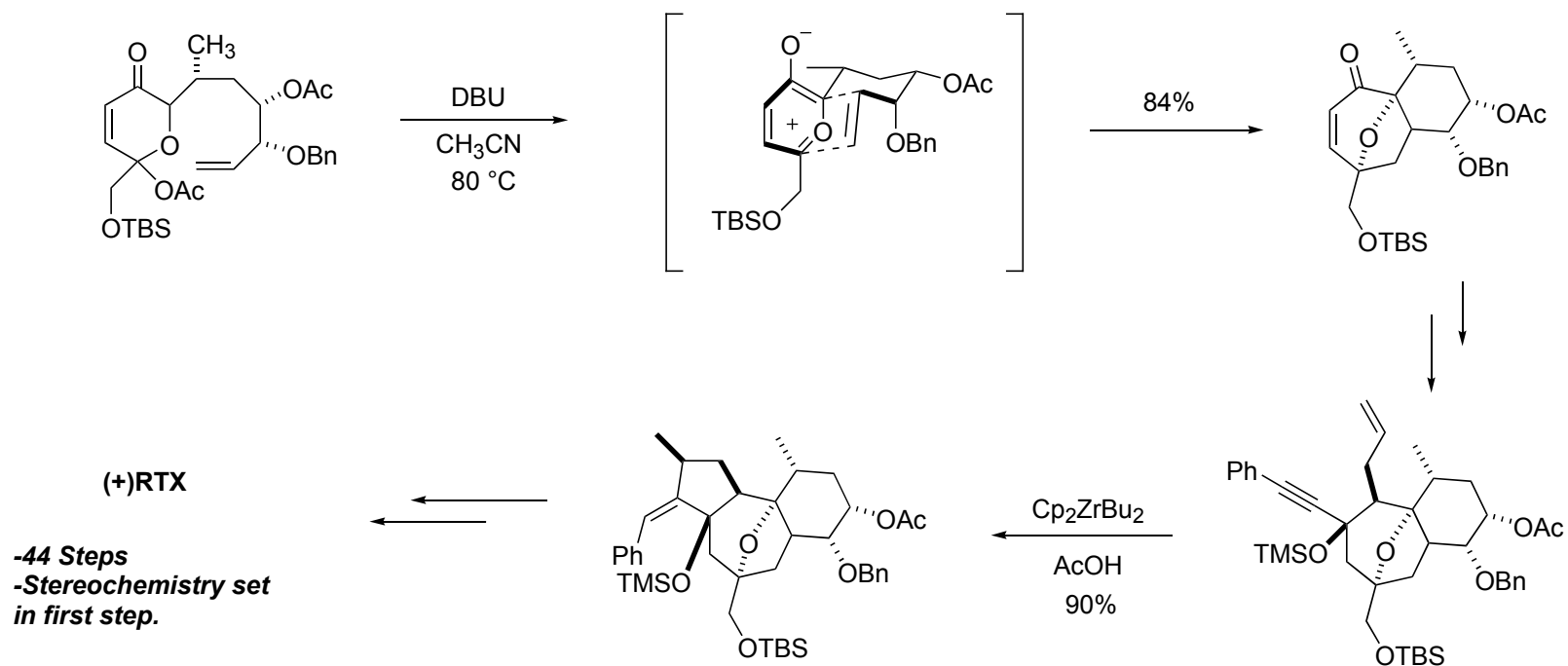
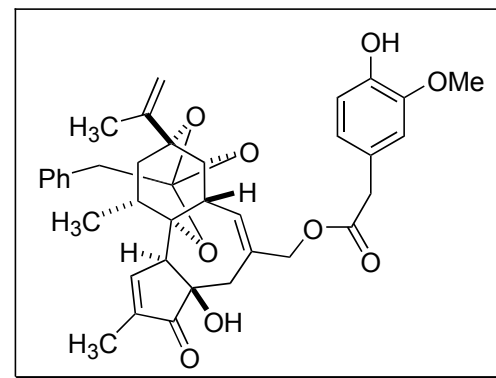
-Excitation of TRPV1 induces the inflow of Na⁺ ions, resulting in pain, and Ca²⁺ buildup. Cytoplasmic calcium buildup seems to desensitize the neurons and is capable of killing the affected neurons.

-RTX and its analogues represent potent pain medications by a) desensitizing the neurons and b) preventing the signalling of pain.

Biochemistry **2004**, 43, 2501

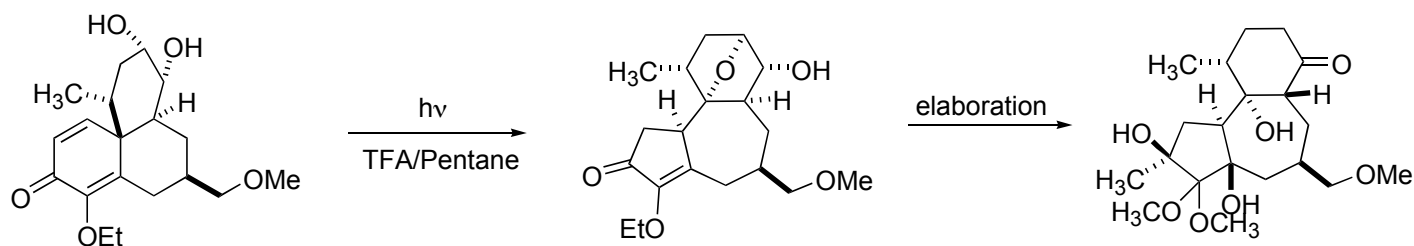
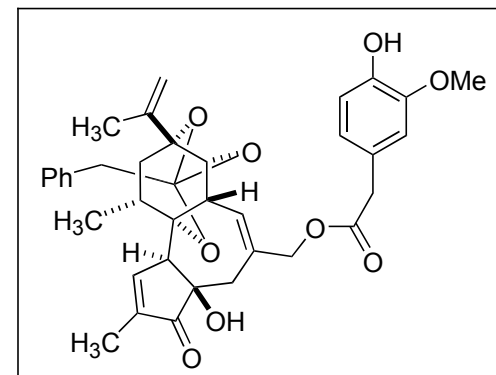
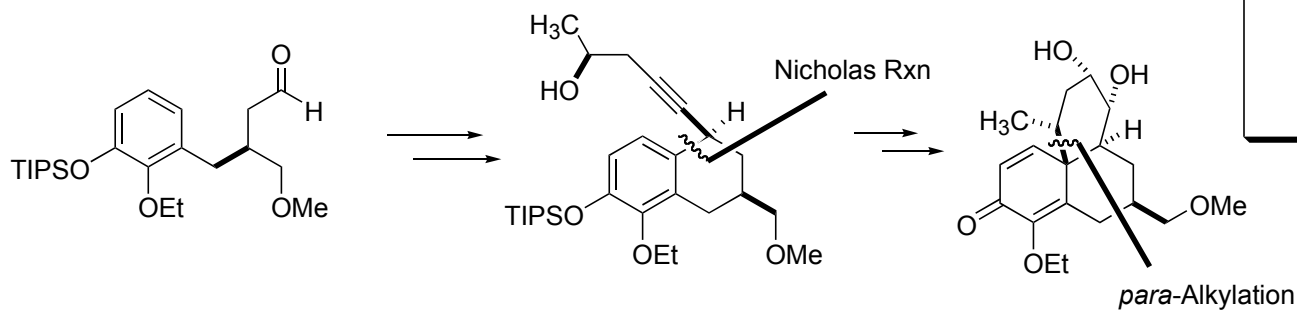
Pain **1996**, 68, 195

Wender's (The First and Only) Synthesis of (+)Resiniferatoxin

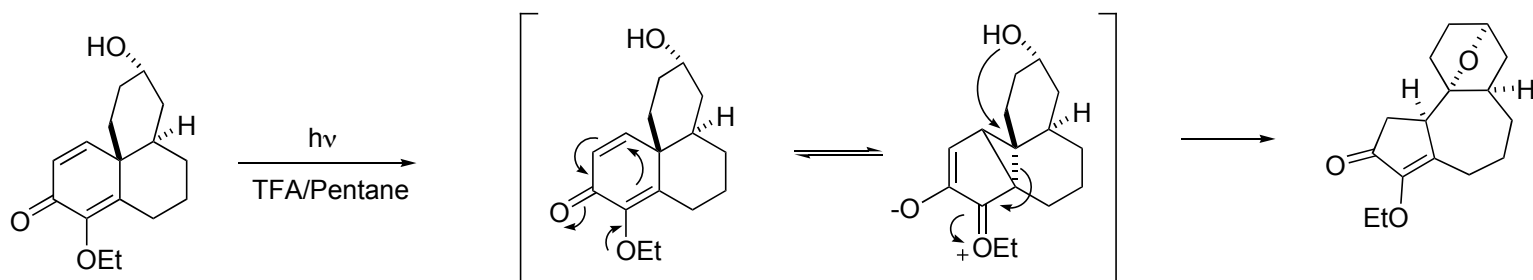


J. Am. Chem. Soc. **1997**, *119*, 12977

Carreira's Initial Approach to the RTX Core

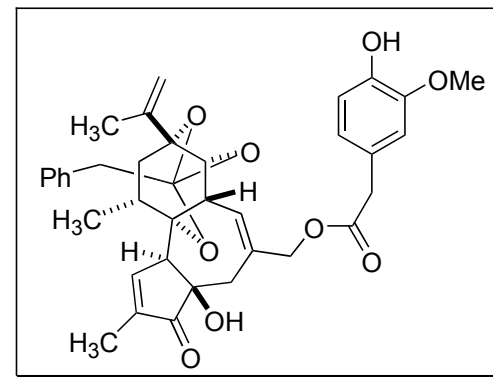
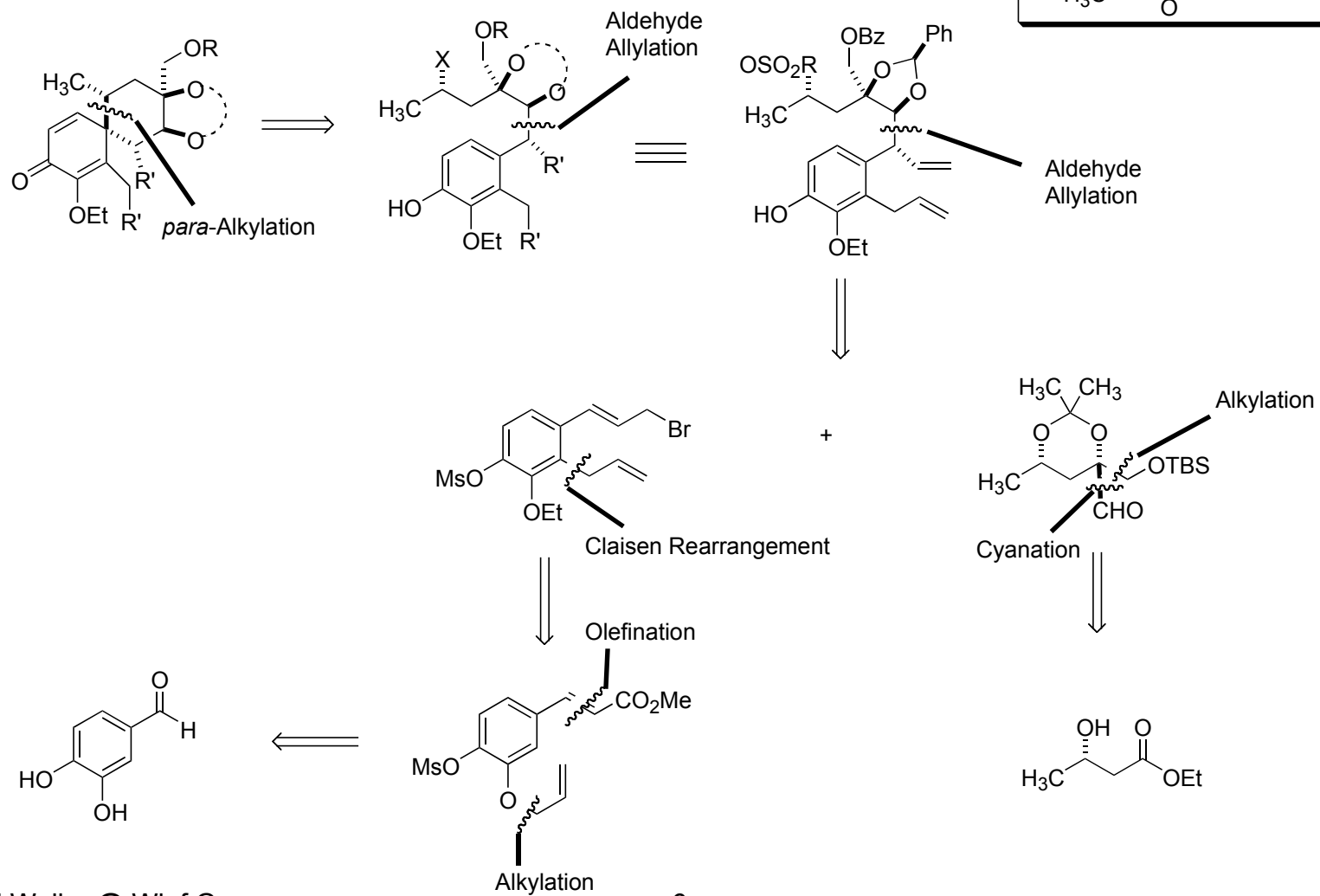


A simplified mechanism

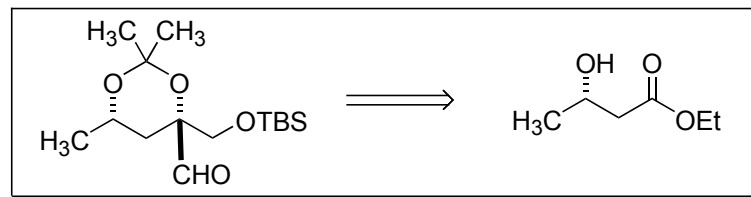


Angew. Chem. Int. Ed. **2001**, *40*, 2694

A Second Approach to the RTX Core



Preparation of Aldehyde Partner



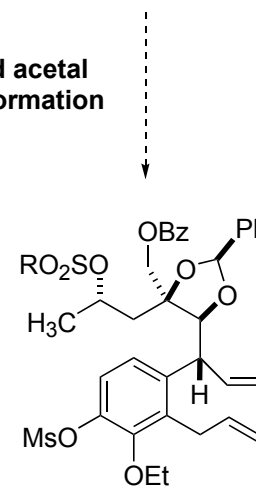
**-Nitrile reduction with DIBAL gave only 30-40% yields
however, the nBuLi aluminate provided aldehyde in 94%**

**-"The reaction sequence could conveniently be
accomplished on a 100 gram scale"**

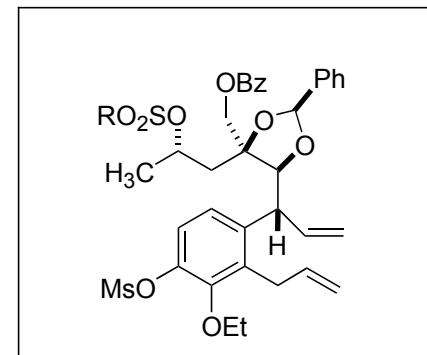
Preparation of Allylating Agent and Allylation



-Only 6-membered to 5 membered acetal rearrangement significant bond formation to arrive at key intermediate.



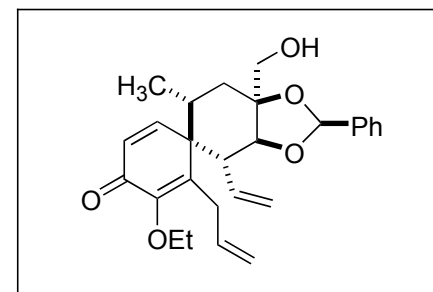
Acetal Rearrangement and the Unexpected Dioxepane Formation



-Unexpected rearrangement attributed to reduced transannular steric demand across the 7 membered ring due to presence of oxygen instead of carbon.

-Dioxepane was utilized without loss of efficiency in route.

A Diastereoselective Phenol para-Alkylation



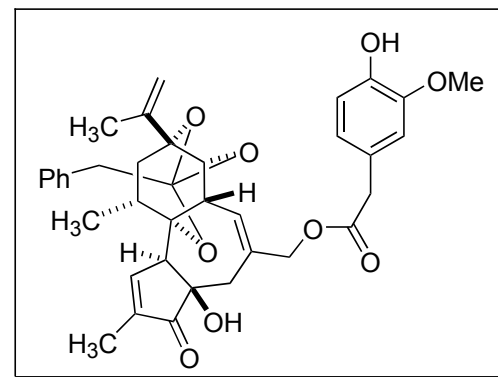
-Solvent mixture and base were crucial. Methanol, ethanol, and isopropanol all gave inferior results (terminal-to-internal olefin isomerization).

-NaOMe, KOtBu, and Cs₂CO₃ all generated isomerization.

-Syn-pentane like interaction disfavors B as functional transition state.

Original reference for alkylation: *J. Am. Chem. Soc.* **1957**, *79*, 756.

Conclusions



-Work is to be continued to see if the aforementioned intermediate undergoes the photocyclic rearrangement.

-What will become of RTX in the clinic?